Remarks

Claims 6 and 22 have been amended to more clearly define the microspheres claimed. No new matter has been introduced. A copy of the claims as amended herein is provided in the enclosed Appendix.

Rejections under the Doctrine of Obviousness-Type Double Patenting

Claims 1-10 and 15-16 were rejected under the doctrine of obviousness-type double patenting as being obvious over claims 1-13 of U.S. Patent No. 5,204,108. Claims 11-14 and 17-28 were rejected under the judicially created doctrine of double patenting.

The Applicant submits that the amended claims are not obvious over the claims of U.S. Patent No. 5,204,108. The amended claims are directed to methods and systems wherein a composition is provided for intranasal systemic delivery of a drug, wherein the composition includes a drug associated with microspheres having a diameter between 0.1 and 10 μm. The claims of U.S. Patent No. 5,204,108 are directed to microspheres adapted to gel in contact with the mucosal surface which are associated with a peptide having a maximum molecular weight of 6000, wherein the microspheres are made of starch, gelatin, collagen or dextran. As discussed in detail below, the Applicant has discovered that the intranasal administration of a microspheres having a diameter between 0.1 and 10 μm in combination with a systemically active drug results in substantially improved systemic delivery of the drug in comparison to the use of larger diameter microspheres. Thus, the

claimed methods and compositions are not obvious in view of the compositions claimed in U.S. Patent No. 5,204,108.

Rejections Under 35 U.S.C. § 112

Claims 6 and 22 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 6 and 22 have been amended to recite a drug delivery composition wherein the microspheres are "heated to stabilize the microspheres" to more clearly recite the claimed composition. Support for the amendment can be found on page 9, lines 9-24, of the specification. As disclosed in the specification, in one embodiment, the microspheres are heated to stabilize them after formation of the microspheres. The Applicant has provided a clear description of heat stabilization of microspheres in the specification and examples of microspheres which can be formed and treated with heat to enhance stability of the microspheres. One of ordinary skill in the art, in view of the teachings of the specification, and knowledge generally available in the art, would readily be able to practice the methods and make the compositions defined by the scope of claims 6 and 22. Thus, the claims as amended are definite. Accordingly, the Applicant requests that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-5, 11 and 13 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 4,847,091 to Illum ("Illum").

Illum

Illum discloses microspheres incorporating sodium cromoglycate which are formed of a material having ion exchange properties. The disclosure of Illum is limited to the synthesis of microspheres incorporating sodium cromoglycate and the use of the microspheres for local treatment. Illum discloses that the microspheres can be used for treatment of allergic conditions. For example, Illum discloses treatment of conditions of the outer eye such as hay fever or conjunctivitis (col. 3, lines 3-20), conditions of the nose such as perennial rhinitis, and conditions of the lung such as asthma. The disclosure of Illum thus is limited to the administration of microspheres for localized treatment of a condition. Nothing in Illum teaches or suggests the use of the sodium cromoglycate containing microspheres for systemic therapeutic treatment.

As noted in the Applicant's Supplemental Response filed May 26, 1994 in the parent application, sodium cromoglycate is poorly absorbed and not useful for systemic treatment. Rather, sodium cromoglycate is used therapeutically for local treatment. As indicated in the Supplemental Response filed May 26, 1994, and in the documents cofiled therewith, sodium cromoglycate is poorly absorbed from the gastrointestinal tract and therefore is only effective when administered for local action. It is used for the treatment of asthma, rhinitis and nasal congestion, which are clearly localized therapeutic treatment applications. Nothing in Illum suggests or teaches systemic delivery of a drug using the microspheres. Illum in fact teaches away from systemic delivery by suggesting only local administration.

Nothing in the disclosure of Illum suggests that the microspheres are capable of systemic delivery of a drug. Nothing in Illum suggests that intranasally administered sodium cromoglycate penetrates nasal tissue and enters the body and is capable of causing a systemic therapeutic effect. Rather, as indicated in Applicant's Supplemental Response filed May 26, 1994, sodium cromoglycate is known to those skilled in the art to be poorly absorbed and to be therapeutically effective only when administered topically for local action. In order for a rejection under 35 U.S.C. § 102 to be proper, all of the material elements of the claims must be present in one prior art source. *In re Marshall* (CCPA 1978) 577 F2d 301. The compositions including microspheres recited in the claims are defined as "capable of systemic delivery of a therapeutically effective amount of the drug to a mammal upon nasal administration," which is not disclosed in Illum.

Illum does not teach or suggest a composition including microspheres including a drug which is systemically active after nasal administration. Nothing in Illum teaches a composition which is capable of systemic delivery of a therapeutically effective amount of a drug upon intranasal administration. Nothing in Illum teaches or suggests methods for administering compositions including microspheres and a drug intranasally to systemically deliver a therapeutically effective amount of a drug. Thus, Illum does not teach or suggest the compositions and methods defined by independent claims 1 or 17. In order for prior art to anticipate a claimed compound on the ground that it is inherently produced in the prior art process, the inherency must be certain. *Ex parte Cyba* (POBA 1966) 155 USPQ 756; *Ex*

parte McQueen (POBA 1958) 123 USPQ 37. The fact that a prior art article may inherently have the characteristics of the claimed product is not sufficient. *Ex parte Skinner* (BPAI 1986) 2 PQ2d 1788. The Applicant has provided evidence including literature articles, in Applicant's Supplemental Response mailed May 26, 1994, indicating that sodium cromoglycate is known to those skilled in the art to be poorly absorbed and to be therapeutically effective only when administered topically for local action. For example, Katzung, Bertram G., "Basic & Clinical Pharmacology," Lange Medical Publications, Los Altos, CA 94022, 1984, states on page 228 that "cromolyn is poorly absorbed from the gastrointestinal tract. For use in asthma, it must be applied topically," and states on page 230 that "because it is so poorly absorbed, adverse effects of cromolyn are minor and are localized in the sites of deposition." Similarly, Martindale (*Extra Pharmacopoeia*, Vol. 30, p. 1142) also enclosed with Applicant's Supplemental Response mailed May 26, 1994 states that sodium cromoglycate is "poorly absorbed" and that "less than 7% of an intranasal dose is absorbed". Thus, nothing in Illum, or in the literature in the area of drug delivery, indicates that the compositions disclosed by Illum, including microspheres and sodium cromoglycate, could be administered intranasally to systemically deliver a therapeutically effective amount of a drug. There is no indication that there is systemic delivery with the Illum compositions. There further is no indication that there is systemic delivery of a therapeutically effective amount of a drug using the Illum compositions.

There also is nothing in Illum which suggests the methods and compositions defined by the dependent claims. Nothing in Illum suggests, for example, compositions including microspheres and a drug consisting of a biologically active peptide such as insulin, as recited in claims 9, 10, 14, 25 and 26. Nothing in Illum suggests a method for systemically delivering a drug in a therapeutically effective amount, as recited in method claims 17-28. In view of Illum and knowledge available in the art, there would have been no motivation to make compositions for systemic delivery of drugs including peptides. In fact, the teachings of Illum and knowledge available in the art would have lead one of ordinary skill away from practicing the claimed methods and making the claimed compositions. For example, as indicated in Gizurarson, *Advanced Drug Delivery Reviews*, Vol. 11, 1993, pp. 331, attached as Exhibit A, nasal administration and systemic delivery of protein drugs in a therapeutically effective amount has proved difficult. Gizurarson states that the absorption and delivery of peptides without adversely effecting the physiology of the nose has proved difficult because absorption of peptide drugs across the nasal mucosa is difficult. Thus, if anything, in view of Illum and knowledge available in the art, one of ordinary skill would have been lead away from the claimed methods and compositions.

The Applicant has demonstrated the synthesis and use of compositions including microspheres which are capable of systemic delivery of a therapeutically effective amount of a drug in a mammal. The Applicant further has provided experimental results which show that the compositions are therapeutically effective systemically. For example, the

compositions can be intranasally administered to systemically deliver insulin to sheep in a therapeutically effective amount to reduce plasma glucose (see Example 3 and, particularly, page 26 of the specification). Nothing in Illum suggests the methods and compositions disclosed in the specification and defined by the precise limitations of the claims. Illum thus does not identically disclose the claimed subject matter, as is required for a proper rejection under 35 U.S.C. § 102. *In re Arkley et al.*, 172 USPQ 524, 526 (CCPA, 1972). Accordingly, the Applicant requests that the outstanding rejections under § 102(e) be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 1-28 were rejected under 35 U.S.C. § 103 as being obvious over Illum, L., *Nato ASI Symposium*, 125:205-210 (1986) "(Illum (1986))". Claims 7-12, 14 and 23-36 were rejected under 35 U.S.C. § 103 as being obvious over Illum or Illum (1986) in view of Hanson *et al.*, *Advanced Delivery Systems for Peptides and Proteins*, p. 233-242 (1988) ("Hanson"), or Salzman *et al.*, *New Eng. J. Med.*, 312:1078-1084 (1985) ("Salzman"), or vice versa.

Illum

As discussed in detail above, nothing in Illum teaches or suggests the methods and compositions recited in the amended claims. Illum does not provide any teaching of, or motivation for, making microspheres for systemic delivery of a therapeutically effective

amount of a drug, or for administering such compositions intranasally to produce a systemic therapeutic effect.

Illum (1986)

Illum (1986) discloses albumin starch microspheres for use in nasal administration. The preferred size range of the microspheres is 40-60 μm (page 207 of Illum 1986). Illum (1986) does not teach or suggest the use of microspheres having a diameter less than 20 μm for use in intranasal delivery. Nothing in Illum (1986) would have motivated one of ordinary skill in the art to make or use the claimed microspheres which have a diameter between 0.1 μm and 10 μm. Illum (1986), in fact, teaches away from the claimed microparticles by suggesting specifically the use of microspheres with a size of 40-60 μm. In view of Illum (1986), there would have been no motivation to make the claimed microspheres.

The Applicant has demonstrated that, unexpectedly, improved systemic therapeutic results are obtained by intranasal administration of microspheres having a diameter less than 10 μm, which is not suggested in the cited art (see Example 1 of the specification). All of the microspheres disclosed in Illum (1986) have a size greater than 10 μm. For example, the albumin microspheres disclosed in Illum (1986) have a swelled size of 40 μm or greater, and since the degree of swelling is 40%, this corresponds to a size of 28 μm or greater. The starch microspheres disclosed in Illum (1986) have a dry volume mean diameter of approximately 20 μm, while the DEAE dextran microspheres obtained from Pharmacia

disclosed in Illum (1986) have a quoted dry bead size ranging from 25 to 125 μm. Thus, nothing in Illum 1986 discloses or suggests making or using the claimed microparticles having a diameter between 0.1 and 10 μm. There is no suggestion in Illum (1986) of the advantages and features of the use of lower diameter microspheres as demonstrated by the Applicant.

Example 1 of the above-identified application provides a comparison of the results of intranasal administration of insulin in starch microspheres of diameter greater than 10 μm and less than 10 μm, which shows that a significant increase in blood insulin concentration was obtained using the smaller (less than 10 μm) microspheres. Example 2 demonstrates that microspheres of 1 to 10 μm have a much longer residence time in the nasal cavity than microspheres of 40 μm, which is unexpected. Example 3 shows that improved intranasal absorption of insulin in sheep was obtained using small (less than 10 μm) hyaluronic acid and hyaluronic acid-dextran microspheres compared to larger microspheres (25 μm) of starch. Applicant further provided additional data, attached as Exhibit 15, together with the Amendment mailed March 21, 1994, in the parent application, demonstrating that the absorption of granulocyte-colony stimulating factor was enhanced using microspheres of 1-10 μm diameter in comparison to larger microspheres.

Thus, nothing in Illum (1986) suggests the unexpected results obtained by the Applicant demonstrating that improved nasal absorption and systemic delivery of a drug can be obtained using microspheres having a diameter between 0.1 and 10 μm. In view of Illum

(1986), one of ordinary skill would have had no motivation to practice the claimed methods or make the claimed compositions. One of ordinary skill in the art would have had no motivation to make compositions including microspheres having a size between about 0.1 and 10 μm to improve intranasal absorption of a drug. Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure. *In re Vaeck* (CAFC 1991) 947 F.2d 488, 20 PQ2d 1438. In the absence of hindsight, there is no suggestion in Illum (1986) of the methods and compositions claimed.

Hanson and Salzman

Hanson discloses that the biological response to nasal administration of calcitonin can be increased by the addition of various surfactants. Salzman discloses that intranasal absorption of insulin can be increased in the presence of a non-ionic detergent. Nothing in Hanson or Salzman suggests the use of microspheres. Nothing in either Hanson or Salzman teaches or suggests making bioadhesive microspheres which have a diameter between 0.1 to 10 μm for the intranasal administration and systemic delivery of a drug. In order to make a determination of obviousness under 35 U.S.C. § 103, the prior art must suggest the invention claimed. *In re Dow Chemical Company*, 837 F.2d 469 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686 (Fed. Cir. 1987). Nothing in Hanson or Salzman provides any suggestion of the claimed compositions including microspheres, or provides any teaching of methods for

making or using the compositions, or any suggestion that they would provide the beneficial effects shown by the Applicant.

Illum, Illum (1986), Hanson and Salzman combined

Nothing in Hanson or Salzman, alone or in combination with Illum and/or Illum (1986), provides any teaching or suggestion of the claimed methods and compositions including microspheres for intranasal administration and systemic delivery of a therapeutically effective amount of a drug. In view of the combined teaches of the applied art, there would have been no motivation or incentive to practice the methods or make the compositions having improved delivery properties claimed.

Nothing in the combined applied art suggests the unexpected results discovered by the Applicant. In deciding obviousness one must look at prior art from the vantage point in time prior to when the invention was made; hindsight obviousness after the invention has been made is not the test. *In re Carroll* (CCPA 1979) 601 F.2d 1184, 202 USPQ 571. In the absence of hindsight, it would not have been obvious to one of ordinary skill in the art to make the claimed compositions or to practice the claimed methods. In order to make a determination of obviousness under 35 U.S.C. § 103, the prior art, viewed by itself and not in retrospect, must suggest doing what the Applicant has done. *In re Shaffer* (CCPA 1956) 229 F.2d 476, 108 USPQ 326; *In re Skoll* (CCPA 1975) 523 F.2d 1392, 187 USPQ 481. The applied art, alone or in combination, does not suggest the compositions or methods defined by the precise limitations of the claims.

Nothing in the applied art suggests the claimed compositions, including microspheres with a diameter between 0.1 and 10 μm and an active drug, which can be intranasally administered to systemically deliver a therapeutically effective amount of the drug to a mammal, as recited in the amended independent claims 1 and 17. Similarly, nothing in the applied art alone or in combination suggests the embodiments defined by the dependent claims wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface (claims 2 and 18), or wherein the microspheres are formed from starch (claims 4 and 20) or certain modified starches (claims 16 and 28). The applied art also does not teach or suggest the compositions defined by the limitations of dependent claims 9-10 and 25-26, wherein the composition includes microspheres and a biologically active peptide such as insulin or calcitonin, and wherein the composition is capable of systemic delivery of a therapeutically active amount of the peptide upon intranasal administration.

Since the applied art, considered either alone or in combination, does not suggest the methods and compositions defined by the limitations of the claims as amended herein, the Applicant requests that the rejections under 35 U.S.C. § 103 be withdrawn.

Conclusion

For all of the forgoing reasons, allowance of each of the pending claims 1-28 as amended herein is respectfully solicited.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Tracy J. Cogborn

Date: March 29, 1996

APPENDIX
Claims as Amended

1. A particulate drug delivery composition for intranasal delivery comprising a plurality of bioadhesive microspheres and a systemically active drug, wherein at least 90 wt % of the microspheres of the composition have a diameter of between 0.1 μm and 10 μm, and wherein the composition is capable of systemic delivery of a therapeutically effective amount of the drug to a mammal upon intranasal administration.

2. A drug delivery composition according to Claim 1 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

3. A drug delivery composition according to Claim 1 or 2 wherein the microspheres comprise starch, gelatin, albumin, collagen, or dextran.

4. A drug delivery composition according to Claim 3 wherein the microspheres are starch microspheres.

5. A drug delivery composition according to Claim 1 wherein the microsphere material is cross-linked.

6. (Twice Amended) A drug delivery composition according to Claim 1 wherein the microspheres have been [treated by heating] heated to stabilize the microspheres.

7. A drug delivery composition according to Claim 1 additionally comprising an absorption enhancer.

8. A drug delivery composition according to Claim 7 wherein the absorption enhancer is a surfactant.

9. A drug delivery composition according to Claim 1 wherein the drug is a biologically active peptide.

10. A drug delivery composition according to Claim 9 wherein the peptide is insulin or calcitonin.

11. A system for intranasal drug delivery comprising a drug delivery composition according to Claim 1 and a container having an orifice through which the composition can be delivered to the nasal mucosa in a gas stream.

12. A system according to Claim 11 wherein the system is such that, in use, the product of the flow rate and the square of the microsphere aerodynamic diameter is greater than 2000 μm^2.litres/min.

13. A method of delivering a drug to the nasal mucosa, comprising introducing a gas stream containing a composition according to Claim 1 into the nose.

14. A method of treating diabetes comprising introducing a gas stream containing a composition according to Claim 1 wherein the systemically active drug is insulin into the nose.

15. The drug delivery composition of claim 1 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

16. The drug delivery composition of claim 1 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.

17. A method for systemically delivering an active drug to a mammal, the method comprising:

a) providing a composition comprising a plurality of bioadhesive microspheres and an active drug, wherein at least 90 wt % of the microspheres in the composition have a diameter between 0.1 μm and 10 μm; and

b) administering the composition to a mammal intranasally thereby to systemically delivery a therapeutically effective amount of the drug to the mammal.

18. The method of claim 17 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

19. The method of claim 17 wherein the microspheres comprise a material selected from the group consisting of starch, gelatin, albumin, collagen and dextran.

20. The method of claim 19 wherein the microspheres comprise starch.

21. The method of claim 17 wherein the microsphere material is cross-linked prior to step b).

22. (Amended) The method of claim 17 wherein the microspheres are [treated by heating] heated to stabilize the microspheres prior to step b).

23. The method of claim 17 the composition provided in step a) further comprises an absorption enhancer.

24. The method of claim 23 wherein the absorption enhancer is a surfactant.

25. The method of claim 17 wherein the drug is a biologically active peptide.

26. The method of claim 25 wherein the peptide is insulin or calcitonin.

27. The method of claim 17 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

28. The method of claim 17 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.

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The relevance of nasal physiology to the design of drug absorption studies

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Contents

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Summary

The parenteral administration of drugs is often associated with complications. For example, low patient acceptance of these routes leading to non-compliance can be a particular risk when self-administration is needed for chronic therapy. Consequently, alternatives such as the nasal, buccal, ocular and vaginal routes have been considered, e.g. for systemic peptide and protein drug delivery. This review focusses on the relevance of the intranasal administration of drugs, peptides and vaccines, and looks at some physiological factors that present a barrier to the use of this route. A brief overview is given of the pharmacokinetics of drugs administered to the nasal cavity, including some of the physiological factors that may influence the kinetics, and on the major intranasal drug absorption models used today. Physiological factors highlighted are (1) mucus and mucociliary clearance; (2) enzymatic degradation; (3) immunological factors; (4) blood flow and (5) deposition of drugs in the nasal cavity.

I. Introduction

Drugs administered intranasally are mainly used to provide a local effect in the nasal mucosa or underlying tissue. Systemic therapy utilising drug absorption from the nasal cavity is not widely practised, but some systemically acting drugs, such as oxytocin, are delivered via the nasal route. Many drugs are readily absorbed from the nasal mucosa; thus, intranasal delivery is capable of providing a rapid systemic response. It was not until the beginning of the 1980's that the nasal route began to attract attention as a potential route for drug delivery [1]. The extensive network of blood capillaries under the nasal mucosa facilitates effective systemic absorption of drugs, including high-molecular-weight drugs such as insulin (6000 Da). This route of administration is likely to have great potential for the future development of, for example, peptide preparations. Unfortunately, the absorption of drugs across the nasal mucosa does not occur to any significant extent in the absence of absorption-promoting agents. Therefore, many studies have been directed towards identifying an efficacious and safe agent to promote the transport of drugs across the nasal mucosa without adversely affecting the physiology of the nose.

The functions of the nose are important in maintaining the health of the individual. Two major functions are olfaction and the conditioning of inspired air for the lungs. The nasal physiology involved in these, and other functions of the nose, should not be damaged by drugs or pharmaceutical excipients. Therefore, the relevance of nasal physiology in the design of drug absorption studies must be considered. Factors affecting nasal physiology during drug administration and the correct choice of animal model is of great importance. Any changes to nasal

physiology must be reversible and toxicological effects must be carefully studied. Exceptions may be permissable when treating life-threatening diseases, where minor changes or damage to the nose may be acceptable. Such products would usually be administered only a few times in a lifetime and, therefore, the benefit to the patient may outweigh the cost to the nasal route.

II. Anatomy of the nose

The nose is divided into two nasal cavities by the median septum; each cavity opens to the face through the nostril and extends posteriorly to the nasopharynx. The cavity is convoluted into the folds of the conchae which engender increased resistance to the airflow, producing intimate contact between inspired air and the mucosa [2]. Because of the large amount of arterial blood flowing in the arteriovenous anastomoses and the large surface area of the respiratory region, it seems likely that the respiratory region is where any significant drug absorption takes place. Absorption may also occur in the olfactory region, possibly directly into the brain, through the olfactory nerve endings [3]. However, in some animals (e.g. rabbit) this region will rarely be exposed to the drug. Variations exist between the olfactory regions of different animal species. In humans and monkeys the olfactory region covers only about 10% (about 10 cm^2) of the mucosal cavity, while in mice and rats it covers about 50% [4] and in the Alsatian dog it covers about 22% (about 170 cm^2) of the nasal cavity [2]. The speed of mucus flow in the olfactory area is nearly zero in humans and monkeys [2,5], but in some animals, such as the rabbit, it is faster than in the respiratory region [6].

The variability of anatomical factors in different species may influence nasal absorption studies. Anatomical characteristics of the most common species studied are summarised in Table I and the anatomy is shown in Fig. 1 [7]. It can been seen

TABLE I

INTERSPECIES COMPARISON OF NASAL CAVITY CHARACTERISTICS, ACCORDING TO CONCHAE COMPLEXITY

Conchae complexity vs. species	Weight (kg)	Nasal volume (ml)	Surface area (cm^2)	Volume to be administered* (µl)	Clearance half-life (min)
Single scroll					
Man	70	20	160	150	15
Monkey	7	8	62	58	10
Double scroll					
Guinea pig	0.6	0.9	27	25	7
Mouse	0.03	0.03	2.8	3	1
Rat	0.25	0.4	14	13	5
Sheep	60	114	327	307	42
Branching					
Dog	10	20	221	207	20
Rabbit	3	6	61	58	10

*Administered per nostril.